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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/546,201	04/10/2000	John M. Polo	PP1463.002	3605

27476 7590 10/19/2005

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/19/2005

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/546,201
Filing Date: April 10, 2000
Appellant(s): POLO ET AL.

Dahna S. Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 29, 2005 appealing from the Office action mailed June 20, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,015,686	DUBENSKY, Jr., et al.	1-2000
WO 90/14090	GILLESPIE et al.	11-1990
5,736,388	CHADA et al.	4-1998

Cella, M. et al. "Maturation and Protection of Dendritic Cells Induced by Double-strand dsRNA" Journal of Experimental Medicine, Vol. 189, no. 5 (March 1999), pp. 821-829.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 26, 28-31 and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubensky, Jr. et al. (US 6,015,686), which is hereinafter referred to as "Dubensky", Cella et al. (Journal of Experimental Medicine. March 1, 1999; 189 (5): 821-829), hereinafter "Cella", Chada et al. (US 5,736,388), hereinafter "Chada" and Gillespie et al. (WO 90/14090), hereinafter "Gillespie".

Claim 26 to require that the double stranded RNA (dsRNA) has self-complementing sequences within the RNA.

Claim 26 has been amended to encompass an expression cassette comprising:

1) a promoter operably linked to a nucleic acid molecule, which when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences, that induces the production of interferon and

2) RNA polymerase II operably linked to a nucleic acid encoding an antigen from a pathogenic agent.

Claims 28 and 29 state that the antigen is a viral antigen selected from HIV, HSV, HBV, HCV, HPV and FIV. Claim 30 states that the pathogenic agent is a bacteria, a parasite or a fungus and claim 31 states that the pathogenic agent is a tumor. Claim 33 requires that the pol II promoter is selected from CMV, SV40, MoMLV LTR and RSV LTR. Claim 34 is drawn to a gene delivery vector comprising the instant expression cassette. Claim 44 is drawn to a cell

containing the gene delivery vector of claim 34. Claims 35-43 state that the vector is a plasmid, a recombinant retrovirus, a recombinant herpesvirus, a recombinant poxvirus, a recombinant adenovirus, a recombinant parvovirus, a recombinant alphavirus, a recombinant polyomavirus, and a eukaryotic layered vector initiation system, respectively.

Dubensky teaches a eukaryotic layered vector initiation system comprising a promoter that expresses a heterologous sequence, see claims 1 and 2. The heterologous sequence is derived from a virus and is selected from HIV, HBV, HCV, FIV, see claim 9, as well as HSV and HPV, see column 4, lines 36-39. Dubensky also teaches that the vector construct can encode proteins from bacteria, parasites or fungus, see column 23, lines 30-36. Additionally, the vector of Dubensky encodes a cancer gene, see column 27, line 60 to column 28, line 2.

The promoter that initiates the synthesis of viral RNA encoding the heterologous gene of Dubensky is selected from the group consisting of the following: CMV, SV40, MoMLV LTR and RSV LTR, see claim 7, column 12, lines 54-62, column 55, lines 14-34, column 100, lines 55-56, column 101, lines 42-57. These promoters are identical to the promoters listed in instant claim 33.

Dubensky teaches that a wide variety of vectors may be utilized in the eukaryotic layered vector initiation system, such as retroviruses, herpesviruses, poxviruses, adenoviruses, parvoviruses, alphaviruses and polyoma viruses, see column 32, lines 26-67. Dubensky also teaches that the expression vector is a plasmid, see column 36, line 44 to column 37, line 16 and column 56, line 47 to column 57, line 11 for example. Dubensky teaches a cell containing the gene delivery vector in claim 12.

Dubensky also teaches that antisense RNA, which forms double-stranded RNA is also utilized in the expression system. The double-stranded RNA increases the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13. Dubensky also claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompass an antisense RNA that forms double-stranded RNA.

Therefore, Dubensky teaches a construct encoding a polymerase II promoter encoding an antigen from a pathogenic agent, as well as a construct encoding a nucleic acid that forms double-stranded RNA for the induction of interferon, see the previous citations.

Dubensky does not teach dsRNA with self-complementing sequences.

However, Gillespie teaches dsRNA with complementing sequences from a vector construct to induce the production of interferon. See page 4, line 10 to page 6, line 18, Figures 1-4 and claims 1-16.

One of ordinary skill in the art at the time the invention was made would have been motivated to express the complementing dsRNA of Gillespie in the vector of Dubensky to induce a therapeutically effective amount of interferon, see claims 9-16 of Gillespie in particular. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of expressing the dsRNA of Gillespie in the vector of Dubensky to induce interferon because both Dubensky and Gillespie express dsRNA from a vector to induce the production of interferon, see the previous citations of both references.

Dubensky does not expressly teach a single construct expressing a heterologous antigen and another promoter encoding a nucleic acid that forms double-stranded RNA.

However, one of ordinary skill in the art at the time the invention was made would have been motivated to express a nucleic acid molecule that forms a complementary-stranded double-stranded RNA (as taught by Gillespie) and a viral antigen in the same construct to stimulate a specific immune response to the viral antigen and to stimulate the production of interferon with dsRNA, see column 37, line 35 to column 38, line 16 and column 23, lines 5-8 of Dubensky and claims 9-16 of Gillespie.

To this same end, Cella states that "dsRNA is a classical inducer of interferon", see the first sentence of the first full paragraph of the second column on page 826. Cella concludes that the loading of viral antigens on MHC class I molecules is optimized by the simultaneous induction of protection and maturation of dendritic cells by dsRNA, see the abstract and the first two paragraphs in the discussion section on page 826. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to simultaneously express dsRNA to and an antigen from the same expression vector to sustain antigen loading in dendritic cells and induce the production of interferon, see page 821, the first two paragraphs in the discussion section on page 826 and the second paragraph of "Sustained Synthesis of Viral Antigens and Class I Molecules Maximizes Antigen Presentation" of Cella.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a construct expressing a heterologous antigen and another promoter expressing a double-stranded RNA in the vector of Dubensky because Dubensky teaches that the expression vector is used to express multiple heterologous sequences, see column 16, line 61 to column 17, line 29 and column 85, line 50 to column 94, line 18 for

example. Therefore, the instant construct would have been prima facie obvious in view of the teachings of Dubensky, absent unexpected results to the contrary.

One of ordinary skill in the art at the time the invention was made would also have been further motivated to express the heterologous sequences of Dubensky from different promoters within the same construct because Chada teach that one promoter within the same construct may be inadequate to ensure an adequate level of expression of all heterologous sequences, see column 26, lines 4-21.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in expressing different heterologous sequences from different promoters in the same construct of Dubensky because the vector of Chada is also a eukaryotic layered vector initiation system, see column 14, lines 52-56. The eukaryotic layered vector initiation system of Chada utilizes the same viral vectors and the same promoters of Dubensky, see column 16, line 48 to column 17, line 21 of Chada. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

(10) Response to Argument

Appellant submits that the Examiner has improperly construed the claims and has used impermissible hindsight reconstruction since the combination of teachings do not result in the claimed subject matter and there is no motivation within the cited references.

In section (a) of the Appeal Brief, Appellant asserts that the term "gene" was used by the Office to describe the claimed dsRNA, a non-coding sequence. Appellant elaborates by

discussing the cited prior art of Dubensky and Chada, which distinguish genes from non-coding sequences.

A review of the summary of the claims presented in file history clearly indicates that the Office repeatedly characterizes dsRNA as a non-coding sequence in the summaries of the claims. See page 3 of the non-final rejection mailed March 7, 2001, page 3 of the non-final rejection mailed December 4, 2001, page 4, of the non-final Office action mailed July 28, 2003, page 3 of the non-final rejection mailed August 19, 2004 and page 3 of the final rejection mailed January 25, 2005. In addition, there is a specific discussion regarding dsRNA as a non-gene on page 3 of the final rejection mailed March 9, 2004. Therefore, Appellant's argument that dsRNA has been mischaracterized as a "gene" by the Office is unsupported. Any mention of "genes" in discussions set forth by the Office intending the multiple expression of heterologous sequences in the vector of Dubensky was inadvertent since Dubensky explicitly teaches expressing more than one heterologous (coding and non-coding) sequence, see column 20, lines 15-25.

Appellant also argues that the Examiner misconstrued the claims to encompass any double stranded RNA, including its formation from an antisense RNA. Appellant reiterates the claim requirement that the dsRNA is formed via self-complementing sequences within the RNA.

In response, originally presented claim 26 did not recite "self-complementing sequences within the RNA". This limitation was presented in the amendment filed June 1, 2004. The requirements set forth by this limitation have been specifically addressed by the teachings of Gillespie in Office actions issued after the new limitation was recited. Therefore, contrary to Appellant's assertions, the limitations presented in the claims have not been misconstrued.

Appellant provides an excerpt from Dubensky, column 23, lines 1-12, and asserts that dsRNA formed from antisense sequences is different from the dsRNA with self-complementing sequences *in vivo*, as required by the claims.

In response, the limitation of "self-complementing sequences within the RNA" is addressed by Gillespie. Dubensky explicitly teach that increased expression of interferon is induced is due to the presence of double-stranded RNA, see column 23, lines 6-8. In addition, Dubensky claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10, which encompasses sequences that produce dsRNA. As acknowledged in previous Office actions, Dubensky does not teach dsRNA with self-complementing sequences, but Gillespie does.

With regard to Gillespie, Appellant asserts that Gillespie merely teaches the formation of self-complementing dsRNA *in vitro* prior to administration and cites excerpts from the reference.

A review of Gillespie clearly indicates that self-complementing dsRNA is recombinantly produced from vectors having promoters placed near the sequence of interest, see page 5, lines 3-8, 25-28 and page 6, lines 5-7. *In vivo* induction of interferon due to the presence of dsRNA formed from the expression of sequences from a vector is encompassed by Dubensky, see column 23, lines 6-8 and claims 1, 10 and 18.

Appellant's argument that the Examiner has ignored any of the limitations in the claims is unfounded.

In section (b) of the Appeal Brief, Appellant argues that the rejection is based on an improper combination of individual elements and cites case law supporting the assertion. More particularly, Appellant argues that none of the references teaches or suggests the instant

invention. With respect to Dubensky, Appellant argues that the reference separates genes from non-genes and does not provide any reason to combine them into a single vector. Appellant argues that there is no suggestion in Dubensky to replace sequences expressing dsRNA for one of the heterologous genes.

Appellant's arguments have been fully considered, but are found unpersuasive. Although Dubensky do not explicitly teach simultaneous expression of a heterologous antigen and sequences that form double-stranded RNA for the induction of interferon, Dubensky certainly suggests this concept. In column 19, line 53 to column 20, line 25, Dubensky states that the "...vector construct may contain additional heterologous or foreign sequences.", see column 19, lines 65-66. Additionally, Dubensky states in column 20, lines 15-25:

"A wide variety of heterologous sequences may be included in the vector construct, including for example sequences which encode...antigens which stimulate an immune response,...as well as antisense sequences (or sense sequences for "antisense applications"). ...[T]he alphavirus vector constructs provided herein may contain (and express, within certain embodiments) two or more heterologous sequences."

This teaching is followed by descriptions of the heterologous sequences (which include antigens and non-coding sequences) recited in column 20, lines 15-25, see column 20, line 26 to column 31, line 39. Therefore, contrary to Appellant's assertions, Dubensky clearly teach expressing multiple heterologous sequences from the vector and that these heterologous sequences are selected from coding and non-coding sequences.

Further, one of ordinary skill in the art at the time the invention was made would have been motivated to express a nucleic acid molecule that forms a complementary-stranded double-

stranded RNA (as taught by Gillespie) and a viral antigen in the same construct to simultaneously induce a specific immune response to a viral antigen, see column 37, line 35 to column 38, line 16, and to stimulate the production of interferon, see column 23, lines 5-8 of Dubensky and claims 9-16 of Gillespie. Cella concludes that the loading of viral antigens on MHC class I molecules is optimized by the simultaneous induction of protection and maturation of dendritic cells by dsRNA, see the abstract and the first two paragraphs in the discussion section on page 826. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to express dsRNA to and a an antigen from the same expression vector to sustain antigen loading in dendritic cells, i.e., induce a specific immune response to a viral antigen, discussed by Dubensky, and induce the production of interferon, see page 821, the first two paragraphs in the discussion section on page 826 and the second paragraph of "Sustained Synthesis of Viral Antigens and Class I Molecules Maximizes Antigen Presentation" of Cella. Therefore, the motivation to express an antigen and dsRNA from the same construct is found within the references themselves.

In section (c), Appellant argues that there is no suggestion to combine the references set forth in the rejection. More specifically, Appellant argues that none of the references teach or suggest in *vivo* production of self-complimenting RNA or that self-complementing RNA and antisense are interchangeable. Referring to Dubensky and Chada, Appellant asserts that there is no reasonable basis for substituting an antisense sequence for a sequence that forms dsRNA via self-complementation. With respect to Gillespie, Appellant argues that since the reference is silent with respect to *in vivo* transcription and Dubensky only produces antisense RNA from a vector, Cella is required to teach about self-complementing RNA expression from vectors.

Appellant's arguments have been fully considered, but are found unpersuasive. Dubensky teaches expressing antisense RNA that forms double-stranded RNA. The double-stranded RNA induces the expression of gamma interferon and boosts the expression of MHC I antigens, see column 23, lines 1-13. Dubensky also claims a vector construct expressing an antisense sequence or a non-coding sequence, see claim 10. The antisense sequence and the non-coding sequence recited in the claim encompasses an antisense RNA or any other non-coding sequence, such as RNA that is self-complementary. Therefore, Dubensky teaches a construct that expresses sequences that form double-stranded RNA for the induction of interferon, see the previous citations.

Dubensky does not teach dsRNA with self-complementing sequences. However, Gillespie teaches dsRNA with complementing sequences from a vector construct to induce the production of interferon. See page 4, line 10 to page 6, line 18, Figures 1-4 and claims 1-16. *In vivo* induction of interferon due to the presence of dsRNA formed from the expression of sequences from a vector is encompassed by Dubensky, see column 23, lines 6-8 and claims 1, 10 and 18. Therefore, both Gillespie and Dubensky teach that dsRNA, whether formed from self-complementing sequences, taught by Gillespie, or antisense RNA specific binding to another RNA molecule, as taught by Dubensky, induces interferon. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of expressing the dsRNA of Gillespie in the vector of Dubensky to induce interferon because both Dubensky and Gillespie express sequences that form dsRNA from a vector to induce the production of interferon, see page 4, line 10 to page 6, line 18 of Gillespie and column 23, lines 1-13 of Dubensky.

In section (d), Appellant argues that the motivation to induce interferon is not sufficient grounds to assert that antisense RNA is an obvious alternative to dsRNA formed by *in vivo* complementation. Applicant supports this assertion because Dubensky indicates that in order to have sufficient large quantities of antisense RNA that is specific for common mRNA transcripts is preferred to produce sufficient quantities of dsRNA to induce interferon production.

Appellant's argument has been fully considered, but is found unpersuasive. To the contrary, this teaching from Dubensky provides further motivation to express the self-complementing dsRNA of Gillespie in the vector of Dubensky for the induction of interferon. In contrast to the antisense RNA of Dubensky, the self-complementary dsRNA of Gillespie does not require any mRNA transcript to be present since the RNA binds to itself. In addition, the amount of dsRNA produced from antisense RNA binding to an mRNA transcript of Dubensky is limited to the number of mRNA transcripts available for antisense binding. However, the quantity self-complementing dsRNA of Gillespie is also not limited to any such considerations since dsRNA is formed directly from expression from a vector.

With respect to Gillespie, Appellant argues that the reference only teaches dsRNA formed by self-complementation and only hypothesizes that these sequences induce interferon. Appellant further argues that Gillespie does not show induction of interferon *in vivo* at therapeutic levels, but teaches that biological activity is assessed once the dsRNA is formed.

A review of Gillespie has been fully considered, but is found unpersuasive. Although Appellant points to page 3, lines 3-5 of Gillespie to support the assertion that the reference only hypothesizes interferon induction with the disclosed dsRNA, the citation pointed to by Appellant states that the invention is drawn to methods of synthesizing stable short dsRNA. There is no

hypothesis that can be located in Gillespie regarding whether dsRNA induces interferon. To the contrary, it is art-recognized that dsRNA induces interferon, see page 1, lines 12-13 of Gillespie and column 23, lines 6-10 of Dubensky. Cella state in the first sentence of the first full paragraph on page 826, that "dsRNA is a classical inducer of type I IFN" and cites reference numbers 28-30 to support this statement. It is noted that reference number 28 was published in 1967. Gillespie does not need to teach or demonstrate the art-recognized properties of dsRNA. In addition, the biological assessments of Gillespie on page 7 are drawn to evaluating antitumor properties, which are separate from the art-recognized property of dsRNA to induce interferon. Claims 9-16 of Gillespie are drawn to various methods of administering self-complementary dsRNA to induce interferon. The dsRNA used in the methods to induce interferon claimed by Gillespie is produced through transcription of self-complementary dsRNA from a plasmid vector within a cell, see page 5, lines 3-8, 25-29, page 6, lines 5-6 and Figure 3 as well as page 7, lines 16-22. *In vivo* expression of dsRNA from a vector cassette to induce interferon is also taught by Dubensky, see column 23 and claims 1, 10 and 18. These explicit teachings provide more than a reasonable expectation of success for producing self-complementing dsRNA *in vivo*.

Appellant concludes that since the references teach that large quantities of dsRNA are required to exhibit biological activity, along with unresolved questions regarding toxicity, the skilled artisan would not have had a reasonable expectation that sufficient quantities of self-complementing dsRNA would induce interferon and would not have viewed that antisense and self-complementing dsRNA are interchangeable. For these reasons, Appellant argues that the rejection should fall.

Appellant's arguments have been fully considered, but are found unpersuasive. As discussed above, the self-complementing dsRNA sequences of Gillespie are not limited to the type or quantity of mRNA transcripts present, as is the antisense RNA of Dubensky, since it is transcribed directly from a vector. Regarding toxicity, the self-complementing dsRNA of Gillespie is also not an issue since these nucleic acids are less toxic than long dsRNA forms, see the abstract of Gillespie. Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to express the self-complementary dsRNA of Gillespie in the expression vector of Dubensky to induce a therapeutically effective amount of interferon, see column 23 of Dubensky and claims 9-16 of Gillespie. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of expressing the dsRNA of Gillespie in the vector of Dubensky to induce interferon because both Dubensky and Gillespie express sequences that form dsRNA from a vector to induce the production of interferon and the vector of Dubensky encompasses expressing any non-coding sequences, see claim 10.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Shanon Foley

Conferees:

James Housel 10/17/05

Christina Chan 10/17/05